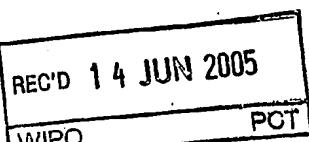


PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

18/8
RTO5

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/EP2005/050403

International filing date (day/month/year)
01.02.2005

Priority date (day/month/year)
04.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07D487/04, C07D519/00, A61K31/439, A61P25/00

Applicant
NEUROSEARCH A/S

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Authorized Officer

Baston, E

Telephone No. +49 89 2399-8229



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/050403

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the International application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - in written format
 - in computer readable form
 - c. time of filing/furnishing:
 - contained in the international application as filed.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/050403

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application,
 claims Nos. 1-43(in part), 43 "with respect to industrial applicability"

because:

- the said international application, or the said claims Nos. 43 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for the whole application or for said claims Nos. 1-43(in part)
 the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

- has not been furnished
 does not comply with the standard

the computer readable form

- has not been furnished
 does not comply with the standard

- the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/050403

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-43(part)
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-43(part)
Industrial applicability (IA)	Yes: Claims	1-42
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.
PCT/EP2005/050403

To section III

Claim 43 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claims (Article 34(4)(a)(I) PCT).

Present claims 1-43 are directed to compounds AZA-X'-A'-Y'-L-Y"-A"-X"-AZA, whereby AZA is defined as being an azabicyclic group according to formulae (A)-(J) and X,A,Y and L are either defined as linker or aromatic or heterocyclic groups. The claims thus cover an extremely large number of compounds, which are essentially only characterized by the two terminal azabicyclic groups which are linked to each other via vaguely defined linking / bridging elements. The application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds having the following definitions for the group AZA:

- 1-Aza-bicyclo[2.2.2]octan
- 1,4-Diaza-bicyclo[3.2.2]nonan

To section V

The following documents were cited in the search report and were considered for the examination of the present application:

- D1: CHRISTOPOULOS, A. ET AL.: "Synthesis and Pharmacological Evaluation of Dimeric Muscarinic Acetylcholine Receptor Agonists" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 298, no. 3, 2001, pages 1260-1268,
- D2: WO 2004/076453 A (NEUROSEARCH A/S; PETERS, DAN; OLSEN, GUNNAR, M; NIELSEN, ELSEBET, OEST) 10 September 2004
- D3: WO 2004/039815 A (PHARMACIA & UPJOHN COMPANY; WONG, ERIK, HO

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.
PCT/EP2005/050403

FONG; CORTES-BURGOS, LUZ, A) 13 May 2004

- D4: WO 02/04442 A (TARGACEPT, INC; BHATTI, BALWINDER, SINGH; CLARK, THOMAS, JEFFREY; MILL) 17 January 2002
D5: EP-A-0 709 381 (ELI LILLY AND COMPANY) 1 May 1996
D6: EP-A-1 282 620 (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; NOVAR) 12 February 2003

The present application is directed to "dimeric" azabicyclic compounds according to general formula (I), which are useful for the treatment of CNS disorders, inflammatory diseases or disorders associated with smooth muscle contraction. This effect is believed to be due to an affinity for nicotinic and / or monoamine receptors. Specially the description contains on page 46 an example which reveals an affinity of example A2 for the alpha7 subtype of nicotinic receptors.

Document D1 discloses already "dimeric" azabicyclic compounds which are also believed to be useful for neurodegenerative diseases due to an affinity for cholinergic receptors. The structures anticipated in D1 (fig. 1) can be distinguished from the claimed ones by the presence of an acetylenic spacer group which is not mentioned in the present application for 'X', 'X" or 'Y', 'Y".

Documents D4-D6 also relate to azabicyclic derivatives which are useful for CNS disorders due to an affinity for cholinergic receptors. However, in these documents no dimeric structures are disclosed.

The requirements of Art. 33(2) PCT are met.

The closest prior art is considered to be represented by document D1, where dimeric structures are already anticipated; D4-D6 disclose a variety of corresponding "monomeric" structures. Thus a person skilled in the art would have been able to combine the teaching of D1 with D4-D6 to arrive at presently claimed structures. The applicant should bear in mind that also the limitation to 1-aza-bicyclo[2.2.2]octan and 1,4-diaza-bicyclo[3.2.2]nonan for AZA cannot be considered as inventive contribution over the prior art, since from document D1 aza-octanes are known. The extremely broad definitions for X', X", Y', Y", A', A" and L will necessarily, for the majority of cases, lead to inactive compounds. Moreover for only one compound activity data were presented. The involvement of an inventive step is

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2005/050403

not acknowledged (Art. 33(3) PCT).

Claim 34 is not clear due to expressions like "cholinergic receptor" or "monoamine receptor" which have to be replaced by well defined pathological conditions (Art. 6 PCT).

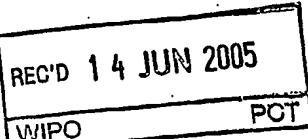
For the assessment of the present claim 43 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

To section VI

The priority document of the present application is not yet available. In case that the presently claimed subject matter is not fully supported by the priority document, D2 and D3 might be relevant for the assessment of novelty and / or inventive step in the national / European phase.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

18/8
PCTOS

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Applicant's or agent's file reference
see form PCT/ISA/220

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/EP2005/050403

International filing date (day/month/year)
01.02.2005

Priority date (day/month/year)
04.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07D487/04, C07D519/00, A61K31/439, A61P25/00

Applicant
NEUROSEARCH A/S

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Authorized Officer

Baston, E

Telephone No. +49 89 2399-8229



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/050403

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the International application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - in written format
 - in computer readable form
 - c. time of filing/furnishing:
 - contained in the international application as filed.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/050403

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application,
- claims Nos. 1-43(in part), 43 "with respect to industrial applicability"
because:
- the said international application, or the said claims Nos. 43 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the whole application or for said claims Nos. 1-43(in part)
- the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|------------------------------------------------------------|
| the written form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
- the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/050403

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-43(part)
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-43(part)
Industrial applicability (IA)	Yes: Claims	1-42
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2005/050403

To section III

Claim 43 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claims (Article 34(4)(a)(I) PCT).

Present claims 1-43 are directed to compounds AZA-X'-A'-Y'-L-Y"-A"-X"-AZA, whereby AZA is defined as being an azabicyclic group according to formulae (A)-(J) and X,A,Y and L are either defined as linker or aromatic or heterocyclic groups. The claims thus cover an extremely large number of compounds, which are essentially only characterized by the two terminal azabicyclic groups which are linked to each other via vaguely defined linking / bridging elements. The application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds having the following definitions for the group AZA:

- 1-Aza-bicyclo[2.2.2]octan
- 1,4-Diaza-bicyclo[3.2.2]nonan

To section V

The following documents were cited in the search report and were considered for the examination of the present application:

- D1: CHRISTOPOULOS, A. ET AL.: "Synthesis and Pharmacological Evaluation of Dimeric Muscarinic Acetylcholine Receptor Agonists" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 298, no. 3, 2001, pages 1260-1268,
- D2: WO 2004/076453 A (NEUROSEARCH A/S; PETERS, DAN; OLSEN, GUNNAR, M; NIELSEN, ELSEBET, OEST) 10 September 2004
- D3: WO 2004/039815 A (PHARMACIA & UPJOHN COMPANY; WONG, ERIK, HO

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.
PCT/EP2005/050403

FONG; CORTES-BURGOS, LUZ, A) 13 May 2004

- D4: WO 02/04442 A (TARGACEPT, INC; BHATTI, BALWINDER, SINGH; CLARK, THOMAS, JEFFREY; MILL) 17 January 2002
D5: EP-A-0 709 381 (ELI LILLY AND COMPANY) 1 May 1996
D6: EP-A-1 282 620 (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; NOVAR) 12 February 2003

The present application is directed to "dimeric" azabicyclic compounds according to general formula (I), which are useful for the treatment of CNS disorders, inflammatory diseases or disorders associated with smooth muscle contraction. This effect is believed to be due to an affinity for nicotinic and / or monoamine receptors. Specially the description contains on page 46 an example which reveals an affinity of example A2 for the alpha7 subtype of nicotinic receptors.

Document D1 discloses already "dimeric" azabicyclic compounds which are also believed to be useful for neurodegenerative diseases due to an affinity for cholinergic receptors. The structures anticipated in D1 (fig. 1) can be distinguished from the claimed ones by the presence of an acetylenic spacer group which is not mentioned in the present application for X',X" or Y',Y".

Documents D4-D6 also relate to azabicyclic derivatives which are useful for CNS disorders due to an affinity for cholinergic receptors. However, in these documents no dimeric structures are disclosed.

The requirements of Art. 33(2) PCT are met.

The closest prior art is considered to be represented by document D1, where dimeric structures are already anticipated; D4-D6 disclose a variety of corresponding "monomeric" structures. Thus a person skilled in the art would have been able to combine the teaching of D1 with D4-D6 to arrive at presently claimed structures. The applicant should bear in mind that also the limitation to 1-aza-bicyclo[2.2.2]octan and 1,4-diaza-bicyclo[3.2.2]nonan for AZA cannot be considered as inventive contribution over the prior art, since from document D1 aza-octanes are known. The extremely broad definitions for X',X",Y',Y",A',A" and L will necessarily, for the majority of cases, lead to inactive compounds. Moreover for only one compound activity data were presented. The involvement of an inventive step is

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2005/050403

not acknowledged (Art. 33(3) PCT).

Claim 34 is not clear due to expressions like "cholinergic receptor" or "monoamine receptor" which have to be replaced by well defined pathological conditions (Art. 6 PCT).

For the assessment of the present claim 43 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

To section VI

The priority document of the present application is not yet available. In case that the presently claimed subject matter is not fully supported by the priority document, D2 and D3 might be relevant for the assessment of novelty and / or inventive step in the national / European phase.